I. Rejection of Claims Under 35 U.S.C. 112, Second Paragraph

Claims 1, 2, 4-10 and 12-20 have been rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner suggests that claim 1 is indefinite in recitation of "specifically hybridizes with" as it is unclear what the antisense is hybridizing with. Applicants have amended claim 1, and by dependency claims 2, 4-10 and 12-15, to recite specific hybridization targets. Accordingly, withdrawal of this rejection is respectfully requested.

II. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 15-20 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. The Examiner suggests that the specification while being enabling for a method of inhibiting MEKK4 expression *in vitro* does not reasonably provide enablement for *in vivo* antisense inhibition

of MEKK4; the Examiner cites several articles to support the position. Applicants respectfully traverse this rejection of the claims.

Applicants disagree with the Examiner's suggestion that cited references on antisense technology support the position that application of antisense *in vivo* is unpredictable.

The Examiner has pointed to several articles on the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of these papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also occur in cells in animals and humans.

The paper by Branch (1998) teaches the need to develop antisense molecules based on sound data and careful screening, such as presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The paper by Green et al. (2000) is another review of the science of antisense and even discusses some of the clinical trials that are ongoing with antisense compounds. Nowhere does the paper

state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The paper by Jen and Gewirtz (2000) also discusses the science of antisense technology and the fact that antisense is one of the tools currently being used to suppress gene expression. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The paper by Agrawal et al. (2000) is another review of the state of the art of antisense technology. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable. In fact, in the conclusions section of the paper, the authors admit that many questions concerning the uptake, distribution, side effects and mechanism of action of antisense oligonucleotides have been answered in recent years.

Development of antisense drug products is viewed by those of skill in the art as being the same as development of any other drug product in terms of applying the basic principles of pharmacology. The key is the careful design of the *in vitro* studies to carefully evaluate dose-response relationships and antisense mechanism, similar to the type of studies presented in the instant specification. Therefore, when antisense oligonucleotides are

developed using well designed studies that progress logically from activity in cells to activity in animals and humans, one of skill would expect that activity in cells would be predictive of activity *in vivo*.

However, Applicant has amended claim 15 to include the limitation that the method is performed *in vitro* in an earnest effort to advance the prosecution and facilitate the allowance of this case. Claims 16-20 have been canceled with Applicant reserving the right to file a continuing application directed to this subject matter without prejudice. Withdrawal of the rejection is requested in light of these amendments.

III. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1, 2 and 4-15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Takekawa et al. (1997), in view of Johnson (US Patent 5,981,265), Johnson (US Patent 6,312,934), Johnson (US Patent 6,333,170), Baracchini et al. (US Patent No. 5,801,154), and Milner et al. (1997). The Examiner suggests it would have been *prima facie* obvious for one of skill to make antisense targeted to MEKK4 based on the sequence taught by Takekawa et al. because the three patents of Johnson teach methods

of making antisense to MEKK nucleic acid molecules, including MEKK4 and Takekawa et al. disclose that these proteins are involved in similar signalling pathways. Further the Examiner suggests that methods for making antisense to a known gene is well known in the art as taught by Milner et al., while methods for modifying antisense as claimed are taught by Baracchini et al., and methods of inhibiting expression of MEKK4 would be obvious based on what is known in the art. The Examiner further suggests that one of skill would have been motivated to make antisense based on the combination of teaching of Takekawa et al. and the Johnson patents, since antisense was well-known in the art, while Baracchini et al. provides motivation to make antisense in the claimed size range as well as with the claimed modifications. The Examiner suggests that expectation of success is provided by the fact that the sequence of MEKK4 was known in the art and screening for antisense was routine (Milner et al.). Applicants respectfully traverse this rejection.

At the outset, Applicants have amended the claims to refer to targeting specific regions of a specific forms of MEKK4 with antisense. Support for these amendments to the claims can be found throughout the specification as filed but in particular at pages 79-82.

Takekawa et al. (1997) disclose the sequence of MEKK4 and its role in the JNK pathway. Nowhere does this paper teach or suggest antisense targeted to specific regions of MEKK4 nucleic acid molecules of SEQ ID NO's 3, 10 or 11, as claimed.

The secondary references cited by the Examiner fail to overcome the deficiencies in teaching of this primary reference.

US Patent 5,981,265 discloses methods for regulating MEKK protein activity by transfecting or transforming a cell with a nucleic acid molecule capable of hybridizing with a nucleic acid molecule consisting of the known MEKK proteins: MEKK1, MEKK2, MEKK3, MEKK4, MEKK5 or MEKK6. Nowhere does this patent teach or suggest that antisense compounds targeted to specific regions of these MEKK nucleic acid molecules. It is only with the teaching of the specification in hand that one of skill would understand that certain regions of the MEKK4 gene would be successful targets for antisense compounds.

US Patent 6,333,170 B1 discloses the general use of antisense as a tool in conjunction with MEKK proteins. No specific antisense compounds are taught or suggested in this patent, nor are any regions of MEKK4 to be specifically targeted with antisense. Again, it is only with the teaching of the specification in hand

that one of skill would understand that certain regions of the MEKK4 gene would be successful targets for antisense compounds.

US Patent 6,312,934 B1 also discloses the general use of antisense as a tool in conjunction with MEKK proteins. Like the other Johnson patents, however, no specific antisense compounds are taught or suggested in this patent, nor are any regions of MEKK4 to be specifically targeted with antisense. Again, it is only with the teaching of the specification in hand that one of skill would understand that certain regions of the MEKK4 gene would be successful targets for antisense compounds.

Milner et al. (1997) teaches a general method for screening antisense molecules. However, nowhere does this paper teach or suggest antisense compounds of any size or type targeted to specific regions of MEKK4 nucleic acid molecules as claimed and their use to inhibit gene expression.

Baracchini et al. teaches modifications of antisense oligonucleotides in general. However, nowhere does this reference teach or suggest antisense compounds of any type targeted to specific regions of MEKK4 nucleic acid molecules as claimed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in

the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the combination of prior art cited fails to teach or suggest the limitations of the claims, which claim antisense compounds targeted to specific regions of a MEKK4 nucleic acid molecule that is listed by sequence, and methods of inhibiting expression of MEKK4, and thus cannot render the instant claimed invention obvious. Further, there is no suggestion in the references cited to combine the teachings of these references as required under MPEP 2143.01. Accordingly, withdrawal of this rejection is respectfully requested.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 11 and 16-20 have been canceled without prejudice.

The claims have been amended as follows:

1. (amended) A compound 8 to 50 nucleobases in length targeted to 5'-untranslated region, a start codon region, a coding region, or a 3'-untranslated region of a nucleic acid molecule encoding MEKK4 of ~~(~~SEQ ID NO: ~~3)~~ 10, a coding region of a nucleic acid molecule encoding MEKK4 of SEQ ID NO: 3, or an exon region of a nucleic acid molecule encoding MEKK4 of SEQ ID NO: 11 , wherein said compound specifically hybridizes with one of said regions and inhibits the expression of MEKK4.

15. (amended) A method of inhibiting the expression of MEKK4 in cells or tissues comprising contacting said cells or tissues *in vitro* with the compound of claim 1 so that expression of MEKK4 is inhibited.